**BACKGROUND:** We investigated whether combination therapy with a statin plus a fibrate, as compared with statin monotherapy, would reduce the risk of cardiovascular disease in patients with type 2 diabetes mellitus who were at high risk for cardiovascular disease. **METHODS:** We randomly assigned 5518 patients with type 2 diabetes who were being treated with open-label simvastatin to receive either masked fenofibrate or placebo. The primary outcome was the first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The mean follow-up was 4.7 years. **RESULTS:** The annual rate of the primary outcome was 2.2% in the fenofibrate group and 2.4% in the placebo group (hazard ratio in the fenofibrate group, 0.92; 95% confidence interval [CI], 0.79-1.08; P=.32). There were also no significant differences between the 2 study groups with respect to any secondary outcome. Annual rates of death were 1.5% in the fenofibrate group and 1.6% in the placebo group (hazard ratio, 0.91; 95% CI, 0.75-1.10; P=.33). Prespecified subgroup analyses suggested heterogeneity in treatment effect according to sex, with a benefit for men and possible harm for women (P=.01 for interaction), and a possible interaction according to lipid subgroup, with a possible benefit for patients with both a high baseline triglyceride level and a low baseline triglyceride level.
level of high-density lipoprotein cholesterol ($P = 0.057$ for interaction). **CONCLUSIONS:** The combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke, as compared with simvastatin alone. These results do not support the routine use of combination therapy with fenofibrate and simvastatin to reduce cardiovascular risk in the majority of high-risk patients with type 2 diabetes. (ClinicalTrials.gov number, NCT00000620.) Copyright 2010 Massachusetts Medical Society.

17. Pending
PURL Review
Date
May 27, 2010

**SECTION 2: CRITICAL APPRAISAL OF VALIDITY**

1. Number of patients starting each arm of the study? 2765 in fenofibrate, 2753 in placebo

2. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)?

   ACCORD overall:
   - **Included:** patients with type 2 diabetes mellitus and an A1c >7.5%
   - **Excluded:**
     - Patients with clinical evidence of cardiovascular (CV) disease who were NOT between 40 and 79 years
     - Patients with subclinical evidence of CV disease or with 2 additional CV factors who were NOT between 55 and 79 years

   Lipid arm:
   - Low-density lipoprotein (LDL) cholesterol 60-180 mg/dL, high-density lipoprotein (HDL) <55 mg/dL for women/blacks

3. Intervention(s) being investigated? Everyone received simvastatin (open-label).

4. Comparison treatment(s), placebo, or nothing? Randomized to receive fenofibrate 160 mg or placebo. Placebo

5. Length of follow up? Mean: 4.7 years

6. What outcome measures are used? List all that assess effectiveness.

   Primary: major CV event (myocardial infarction, cerebrovascular accident, CV death).

7. What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CI, p-values, etc.

   Primary outcome: ARR: 0.7% (NS), NNT: 135 (NS).

8. What are the adverse effects of intervention compared with no intervention?

   Possible increase in serum creatinine with fenofibrate.

9. Study addresses an appropriate and clearly focused question - select one

   Well covered

10. Random allocation to comparison groups

    Well covered
11. Concealed allocation to comparison groups
Well covered

12. Subjects and investigators kept “blind” to comparison group allocation
Well covered

13. Comparison groups are similar at the start of the trial
Well covered

14. Were there any differences between the groups/arms of the study other than the intervention under investigation? If yes, please indicate whether the differences are a potential source of bias.
Well covered

15. Were all relevant outcomes measured in a standardized, valid, and reliable way?
Yes

16. Are patient-oriented outcomes included? If yes, what are they?
Yes: death, CV events.

17. What percent dropped out, and were lost to follow up? Could this bias the results? How?
Does not seem to be addressed, other than to note that 80% were taking study medications as directed at the end of the study.

18. Was there an intention-to-treat analysis? If not, could this bias the results? How?
Yes

19. If a multi-site study, are results comparable for all sites?
Yes

20. Is the funding for the trial a potential source of bias? If yes, what measures were taken to insure scientific integrity?
Several Pharma companies had ties, no specific disclosure was made about control of data.

21. To which patients might the findings apply? Include patients in the study and other patients to whom the findings may be generalized.
Patients with type 2 diabetes mellitus who have high triglycerides, low HDL, and high risk for CV disease.

22. In what care settings might the findings apply, or not apply?
Primary care, cardiology
23. To which clinicians or policy makers might the findings be relevant?

SECTION 3: REVIEW OF SECONDARY LITERATURE

1. DynaMed excerpts


3. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)

This article (potential PURL) applies only to people with diabetes who are also taking statins.

4. UpToDate excerpts


7. PEPID PCP excerpts

Fibrates (fibric acids)

- Gemfibrozil 600 mg BID, fenofibrate (Lofibra 200 mg QD, TriCor 145 mg QD), clofibrate 1 g BID
- Inhibit peripheral lipolysis, decrease hepatic excretion of free fatty acids
- LDL decrease 0%-20%, HDL increase 10%-20%, triglyceride (TG) decrease 20%-50%
- Side effects:
  - Dyspepsia, gallstones, liver toxicity, myopathy (more often when taken with statin)
- Contraindications
  - Absolute: severe renal/hepatic disease
  - Relative: history of hepatitis, alcoholism, pregnancy, breastfeeding
- Combination with statins
  - LDL decrease >40%, HDL increase 20%, TG decrease >50%
  - Increased risk of myopathy
    - Greater with gemfibrozil than fenofibrate

8. PEPID citation/access data


9. PEPID content updating

1. Do you recommend that PEPID get updated on this topic?
Yes, there is important evidence or recommendations that are missing

If yes, which PEPID Topic, Title(s):
Dyslipidemias: drug therapy

2. Is there an EBM Inquiry (HelpDesk Answers and Clinical Inquiries) as indicated by the EB icon (estruction) that should be updated on the basis of the review?
Yes, there is important evidence or recommendations that are missing

If yes, which Evidence Based Inquiry(HelpDesk Answer or Clinical Inquiry), Title(s):
SECTI0N 4: CONCLUSIONS

1. **Validity:** How well does the study minimize sources of internal bias and maximize internal validity? Give one number on a scale of 1 to 7 (1=extremely well; 4=neutral; 7=extremely poorly)

2. If 4.1 was coded as 4, 5, 6, or 7, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?

3. **Relevance:** Are the results of this study generalizable to and relevant to the health care needs of patients cared for by “full scope” family physicians? Give one number on a scale of 1 to 7 (1=extremely well; 4=neutral; 7=extremely poorly)

4. If 4.3 was coded as 4, 5, 6, or 7, please provide an explanation.

5. **Practice-changing potential:** If the findings of the study are both valid and relevant, does the practice that would be based on these findings represent a change from current practice? Give one number on a scale of 1 to 7 (1=definitely a change from current practice; 4=uncertain; 7=definitely not a change from current practice)

6. If 4.5 was coded as 1, 2, 3, or 4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.

7. **Applicability to a Family Medical Care Setting:** Is the change in practice recommendation something that could be done in a medical care setting by a

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In the University of Chicago group, no one routinely uses fibrates in combination with statins to increase HDL or decrease TG for the prevention of CV disease. We question whether this is a practice-changing recommendation.

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In the University of Chicago group, no one routinely uses fibrates in combination with statins to increase HDL or decrease TG for the prevention of CV disease. We question whether this is a practice-changing recommendation.
family physician (office, hospital, nursing home, etc), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, educating or counseling a patient; or creating a system for implementing an intervention? Give one number on a scale of 1 to 7 (1=definitely could be done in a medical care setting; 4=uncertain; 7=definitely could not be done in a medical care setting)

8. If you coded 4.7 as a 4, 5, 6 or 7, please explain.

9. Immediacy of Implementation: Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug or other essentials available on the market? Give one number on a scale of 1 to 7 (1=definitely could be immediately applied; 4=uncertain; 7=definitely could not be immediately applied)

10. If you coded 4.9 as 4, 5, 6, or 7, please explain why.

11. Clinical meaningful outcomes or patient-oriented outcomes: Are the outcomes measured in the study clinically meaningful or patient oriented? Give one number on a scale of 1 to 7 (1=definitely clinically meaningful or patient oriented; 4=uncertain; 7=definitely not clinically meaningful or patient oriented)

12. If you coded 4.11 as a 4, 5, 6, or 7, please explain why.

13. In your opinion, is this a Pending PURL? Give one number on a scale of 1 to 7
Criteria for a Pending PURL:

- Valid: Strong internal scientific validity; the findings appears to be true.
- Relevant: Relevant to the practice of family medicine
- Practice changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice.
- Applicability in medical setting:
- Immediacy of implementation

14. Comments on your response in 4.13

It seems like a very limited recommendation (limited to patients with diabetes mellitus at high risk already on a statin but not a high-dose statin); it is also a recommendation AGAINST doing something (feels like the standard should be high for a null trial).

SECTION 5: EDITORIAL DECISIONS

1. FPIN PURLs editorial decision (select one)
   Pending PURL

2. Follow up issues for Pending PURL Reviewer

3. FPIN PURLS Editor making decision
   Kate Rowland

4. Date of decision
   May 27, 2010

5. Brief summary of decision
   In the University of Chicago group, no one was routinely using fibrates in combination with statins to increase HDL or decrease TG for the prevention of CV disease. We questioned whether this was a practice-changing recommendation.